Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V

Isatuximab (new therapeutic indication: multiple myeloma, first-line, ineligible for stem cell transplant, combination with bortezomib, lenalidomide and dexamethasone)

of 7 August 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company have conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient isatuximab (Sarclisa) was listed for the first time on 1 February 2021 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 20 January 2025, isatuximab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 5 February 2025, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company have submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with

Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient isatuximab with the new therapeutic indication

"SARCLISA is indicated in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant." .

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 May 2025 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of isatuximab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA have evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of isatuximab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Isatuximab (Sarclisa) in accordance with the product information

SARCLISA is indicated in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

Therapeutic indication of the resolution (resolution of 07.08.2025):

See new therapeutic indication according to marketing authorisation.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

Appropriate comparator therapy for isatuximab in combination with bortezomib, lenalidomide and dexamethasone:

– Daratumumab in combination with lenalidomide and dexamethasone

or

– daratumumab in combination with bortezomib, melphalan and prednisone

or

– bortezomib in combination with melphalan and prednisone

or

– bortezomib in combination with lenalidomide and dexamethasone

or

– thalidomide in combination with melphalan and prednisone

or

– bortezomib in combination with cyclophosphamide and dexamethasone [only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Annex VI to Section K of the Pharmaceuticals Directive]

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.

4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

On 1. In addition to isatuximab, the following active ingredients are approved in the present therapeutic indication:

bendamustine, carmustine, cyclophosphamide, doxorubicin, melphalan, vincristine, bortezomib, daratumumab, lenalidomide, thalidomide, dexamethasone, prednisolone and prednisone.

Some of the marketing authorisations are tied to (specific) concomitant active ingredients. In addition, the combination of bortezomib, cyclophosphamide and dexamethasone can be prescribed off-label.

On 2. According to the therapeutic indication, patients are ineligible for autologous stem cell transplant. A non-medicinal treatment option is not considered as a appropriate comparator therapy for the therapeutic indication in question.

On 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Daratumumab – resolution of 16 May 2024 (combination with bortezomib, melphalan and prednisone)
- Daratumumab – resolution of 18 March 2022 (combination with lenalidomide and dexamethasone)

Annex VI to Section K of the Pharmaceuticals Directive - prescribability of approved medicinal products in non-approved therapeutic indications (off-label use):

- Bortezomib plus cyclophosphamide plus dexamethasone for the induction therapy of newly diagnosed multiple myeloma (resolution of 20 May 2021)

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V. Written statements from the AkdÄ as well as the German Society for Haematology and Medical Oncology (DGHO) are available.

Among the approved active ingredients listed under 1), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of care.

The available evidence on the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant recommends trio or tetra combination therapies based on an immunomodulator and/or proteasome inhibitor. In this regard, the combination therapies bortezomib + melphalan + prednisone, thalidomide + melphalan + prednisone, lenalidomide + melphalan + prednisone and the combination therapy bortezomib + lenalidomide + dexamethasone can be considered according to the authorisation status. The dual combination of lenalidomide + dexamethasone is therefore not defined as an appropriate comparator therapy.

In addition, two combination therapies based on the CD38 antibody daratumumab are approved for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. By resolution of 16 May 2024, the G-BA determined an indication of a considerable additional benefit of the combination therapy of daratumumab + bortezomib + melphalan + prednisone, compared to a combination therapy according to doctor's instructions. By resolution of 18 March 2022, the G-BA identified a hint for a considerable additional benefit of the combination therapy daratumumab + lenalidomide + dexamethasone compared to lenalidomide + dexamethasone. Both combination therapies have found their way into current guidelines.

The evidence for the combination therapy of lenalidomide + melphalan + prednisone is inferior overall compared to the other combination therapies. In contrast to bortezomib or thalidomide + melphalan + prednisone, no advantage compared to melphalan + prednisone was shown with regard to survival. Lenalidomide + melphalan + prednisone is therefore not determined in the present therapeutic indication as an appropriate comparator therapy.

Furthermore, the combination therapy of bortezomib, cyclophosphamide and dexamethasone can be prescribed off-label for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy in the therapeutic indication of newly diagnosed multiple myeloma, irrespective of the eligibility for stem cell transplant. This combination is also recommended in the available evidence.

The combination of daratumumab + bortezomib + lenalidomide + dexamethasone is another approved treatment option in this therapeutic indication. The active ingredient has not yet been the subject of a benefit assessment according to Section 35a SGB V. Based on the generally recognised state of medical knowledge, the combination therapy of daratumumab + bortezomib + lenalidomide + dexamethasone was therefore not determined to be an appropriate comparator therapy.

Overall, the combinations mentioned in the appropriate comparator therapy are equally appropriate comparator therapies.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of isatuximab is assessed as follows:

Adults with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

Hint for a minor additional benefit

Justification:

The pharmaceutical company has submitted results from the open-label, randomised, controlled phase III IMROZ study for the benefit assessment.

The ongoing IMROZ study compares isatuximab in combination with bortezomib + lenalidomide + dexamethasone (Isa-VRd regimen) with bortezomib + lenalidomide + dexamethasone (VRd regimen).

The study is divided into a global cohort and a China expansion cohort. Evaluations of the global cohort are used for the present benefit assessment, as the China expansion cohort is not relevant for the benefit assessment due to its small percentage. A total of 446 patients

were enrolled in the study and randomised in a 3:2 ratio to the two study arms (N=265 Isa-VRd arm; N=181 VRd arm). The study that has been ongoing since 07.12.2017 in study sites in Europe, North America and Asia is scheduled to run until 30.06.2027.

A total of three data cut-offs are planned, one of which is currently available. The first data cut-off (for the endpoint categories of mortality, morbidity and health-related quality of life from 26.09.2023 and side effects from 03.10.2023) is used for the present benefit assessment. This data cut-off is based on the time point at which 162 PFS events (approx. 75% of the expected PFS events) were reached.

On the eligibility criteria for autologous stem cell transplant (ASCT) in the IMROZ study

According to the inclusion criteria of the study, patients must be aged 65 years and older or have significant comorbidities to be deemed ineligible for autologous stem cell transplant (ASCT). Since the start of the study, the generally recognised state of medical knowledge regarding eligibility for ASCT has evolved, with biological age, taking into account relevant comorbidities, becoming more important than chronological age. As a result, patients may have been enrolled in the study who would be suitable for ASCT according to the generally recognised state of medical knowledge. To counter this, the pharmaceutical company presented a sensitivity analysis that takes into account the criticism of the European Medicines Agency (EMA) from the marketing authorisation procedure for daratumumab. In this regard, the sub-population "ASCT ineligibility according to EMA definition" includes patients with age ≥ 70 years, comorbidities or Eastern Cooperative Oncology Group Performance Status (ECOG-PS) = 2. These criteria are met by 74% of patients in the total population.

For the total populations as well as for the post hoc defined sub-population, the uncertainty arises that the percentage of patients who would actually not have been eligible for ASCT is unclear. The procedure chosen by the pharmaceutical company to operationalise the sub-population (ASCT ineligibility) is understandable and is considered to be a sufficient approximation to the target population. Nevertheless, the resulting sub-population and the total population are subject to uncertainty, as the assessment of ASCT ineligibility would have to be patient-individual and independent of chronological age. Due to relevant differences in the results of relevant endpoints between the subgroups of ASCT ineligibility and eligibility, the total population of the IMROZ study cannot be used in the present benefit assessment. Instead, the sub-population formed by the pharmaceutical company is used, as this represents a better approximation of the target population.

Extent and probability of the additional benefit

Mortality

Overall survival in the IMROZ study was operationalised as the time from randomisation to death from any cause. For the endpoint of overall survival, there was no statistically significant difference between the treatment arms.

Morbidity

Progression-free survival (PFS)

Progression-free survival is operationalised in the IMROZ study as the time from randomisation to the time of first documented disease progression (according to the Independent Review Committee (IRC)) or the time of death from any cause, whichever occurs first. The response is determined according to the IMWG criteria.

For the PFS endpoint, there was a statistically significant advantage of isatuximab + bortezomib + lenalidomide + dexamethasone.

The present PFS endpoint is a composite endpoint consisting of endpoints from the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "disease progression" was assessed according to IMWG criteria and thus, not in a symptom-related manner but only by means of laboratory parametric, imaging, and haematological procedures.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the extent of the additional benefit remains unaffected.

EORTC-QLQ C30

In the IMROZ study, disease symptomatology was assessed using the cancer-specific EORTC-QLQ C30 questionnaire. The symptom scales include dyspnoea, nausea and vomiting, appetite loss, fatigue, pain, insomnia, constipation and diarrhoea. In addition, the additional module EORCT QLQ-MY20 was used in the study with the endpoints of disease symptoms and side effects.

In the dossier, the pharmaceutical company presented responder analyses for the time to first deterioration and the time to permanent deterioration by ≥ 10 points.

In the present data basis, in which the duration of observation of all patient-reported endpoints differs significantly between the study arms, the analyses of the time to first deterioration are used in the present benefit assessment.

For the dyspnoea symptom, the study showed a statistically significant difference to the advantage of isatuximab + bortezomib + lenalidomide + dexamethasone.

In addition, for the symptoms of nausea and vomiting as well as appetite loss, there was a statistically significant difference to the advantage of isatuximab + bortezomib + lenalidomide + dexamethasone.

For each of the remaining symptoms of fatigue, pain, insomnia, constipation and diarrhoea, there was no statistically significant difference between the treatment arms.

EORCT QLQ-MY20

For each of the endpoints of disease symptoms and side effects, measured using the EORCT QLQ-MY20, there was no statistically significant difference between the treatment arms.

To summarise, an overall improvement in symptomatology can be observed. Taking into account the extent and clinical relevance, the advantage in the endpoint of dyspnoea is considered to be a relevant result, and the advantage in the endpoint of nausea and vomiting is considered to be another relevant result.

Health status according to EQ-5D VAS

Health status is assessed in the present study using the EQ-5D visual analogue scale (VAS). For the present benefit assessment, the time to first deterioration in health status by ≥ 15 points is used.

For the health status, there was no statistically significant difference between the treatment arms.

Quality of life

EORTC-QLQ C30

Health-related quality of life is assessed in the IMROZ study using the functional scales of the EORTC-QLQ C30 and the EORCT QLQ-MY20 additional module (future prospects, body image).

In the dossier, the pharmaceutical company presented responder analyses for the first deterioration and the permanent deterioration in health-related quality of life respectively by ≥ 10 points.

In the present data basis, in which the duration of observation of all patient-reported endpoints differs significantly between the study arms, the analyses of the time to first deterioration are used in the present benefit assessment.

For the role functioning, there was a statistically significant difference to the advantage of isatuximab + bortezomib + lenalidomide + dexamethasone. For each of the remaining functional scales using EORTC-QLQ C30 (global health status, physical functioning, emotional functioning, cognitive functioning, social functioning), there was no statistically significant difference between the treatment arms.

For the future prospects, assessed using the EORCT QLQ-MY20, there was a statistically significant difference to the advantage of isatuximab + bortezomib + lenalidomide + dexamethasone. For the body image, there was no statistically significant difference between the treatment arms.

Overall, there was an advantage for the endpoint category of health-related quality of life due to improvements in the endpoints of role functioning and future prospects.

Side effects

Serious adverse events (SAEs) and severe AEs:

For the endpoints of SAEs and severe AEs, there were no statistically significant differences between the treatment arms of the study.

Therapy discontinuation due to AEs

With regard to the analyses submitted by the pharmaceutical company in the written statement procedure, which dispel the uncertainties of the analyses presented in the dossier, there was no statistically significant difference between the treatment arms.

Specific adverse events:

Infusion-related reactions

For the endpoint of infusion-related reactions, no suitable aggregated analyses of the underlying symptoms are available. As part of the written statement procedure, the pharmaceutical company submitted analyses for adverse events based on the SOCs and PTs, which took into account the underlying symptoms of the infusion-related reactions. This addresses the uncertainties described in the dossier assessment regarding further potential disadvantages for the non-severe/ non-serious specific adverse events. These analyses do not result in any relevant changes compared to the analyses already presented in the dossier.

Peripheral neuropathy

For the endpoint of peripheral neuropathy, corresponding analyses were subsequently submitted by the pharmaceutical company as part of the written statement procedure, which dispel the uncertainties of the analyses submitted in the dossier. There was no statistically significant difference between the treatment arms.

Metabolism and nutrition disorders (SOC, severe AEs) and respiratory, thoracic and mediastinal disorders (SOC, severe AEs)

For each of the endpoints of metabolism and nutrition disorders (SOC, severe AEs) and respiratory, thoracic and mediastinal disorders (SOC, severe AEs), there was a statistically significant difference to the advantage of isatuximab + bortezomib + lenalidomide + dexamethasone.

Conclusion on side effects:

In the overall assessment, there were no statistically significant differences between the treatment arms in the endpoint category of side effects for SAEs, severe AEs, and discontinuations due to AEs. In detail, individual specific AEs (metabolism and nutrition disorders and respiratory, thoracic and mediastinal disorders) show advantages of isatuximab + bortezomib + lenalidomide + dexamethasone. In view of the fact that no statistically significant differences were observed for the overall rates of AEs, SAEs and severe AEs, these advantages were considered inadequate to reach a conclusion other than that there was no relevant difference overall for the endpoint category of side effects.

<u>Overall assessment</u>

Results on mortality, morbidity, quality of life and side effects are available from the IMROZ study for the assessment of the additional benefit of isatuximab in combination with bortezomib, lenalidomide and dexamethasone, compared to the combination therapy of bortezomib + lenalidomide + dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. The results for a sub-population (ASCT ineligibility) are used for the benefit assessment.

There was no significant difference between the study arms in terms of overall survival.

For the symptomatology, assessed using the EORTC QLQ-C30 and EORTC QLQ-MY20, an overall advantage of isatuximab + bortezomib + lenalidomide + dexamethasone can be determined due to an improvement, particularly in the endpoints of dyspnoea, nausea and vomiting .

For the health-related quality of life, assessed using the EORTC QLQ-C30 and EORTC QLQ-MY20, there were improvements in role functioning and future prospects, which is why an overall advantage of isatuximab + bortezomib + lenalidomide + dexamethasone could be identified.

With regard to the endpoint category of side effects, there were no statistically significant differences between the treatment arms for the overall rates of severe AEs, SAEs and discontinuation due to AEs. In detail, there were advantages of isatuximab + bortezomib + lenalidomide + dexamethasone for individual specific AEs (metabolism and nutrition disorders and respiratory, thoracic and mediastinal disorders). In view of the fact that no statistically significant differences were observed for the overall rates of AEs, SAEs and severe AEs, these advantages were considered inadequate to reach a conclusion other than that there was no relevant difference overall for the endpoint category of side effects.

In the overall assessment, the G-BA identified a minor additional benefit of isatuximab in combination with bortezomib, lenalidomide and dexamethasone compared with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, open-label, controlled phase III IMROZ study.

At the study level, the risk of bias is considered low. However, there were significant uncertainties as the study also includes patients who could be eligible for ASCT according to current eligibility criteria. The information required to fully eliminate these uncertainties can no longer be determined post hoc.

For the overall survival, the risk of bias at the endpoint level is rated as low. In the patient-reported endpoints on morbidity and health-related quality of life, the lack of blinding in subjective endpoint assessment leads to a high risk of bias.

Taking into account the uncertainties mentioned above, an overall hint for the identified additional benefit can be derived.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient isatuximab:

"Isatuximab is indicated in combination with bortezomib, lenalidomide and dexamethasone , for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant."

As the appropriate comparator therapy, the G-BA determined various combination therapies as alternative comparator therapies, including bortezomib in combination with lenalidomide and dexamethasone. For the benefit assessment, the pharmaceutical company presented the results of the ongoing, open-label, randomised IMROZ study, in which bortezomib in combination with lenalidomide and dexamethasone was used in the comparator arm.

There was no significant difference between the study arms in terms of overall survival.

For the symptomatology, an overall advantage of isatuximab + bortezomib + lenalidomide + dexamethasone can be determined due to an improvement, particularly in the endpoints of dyspnoea, nausea and vomiting .

For the health-related quality of life, there were improvements in role functioning and future prospects, which is why an overall advantage of isatuximab + bortezomib + lenalidomide + dexamethasone could be identified.

With regard to the endpoint category of side effects, there were no statistically significant differences between the treatment arms for the overall rates of severe AEs, SAEs and discontinuation due to AEs. In detail, there were favourable effects of isatuximab + bortezomib + lenalidomide + dexamethasone for individual specific AEs, but these are considered inadequate to determine an overall relevant difference in side effects.

In the overall assessment, the G-BA identified a minor additional benefit of isatuximab in combination with bortezomib, lenalidomide and dexamethasone compared with bortezomib, lenalidomide and dexamethasone.

The reliability of data is classified as a "hint" due to the uncertainties in relation to the study population and the risk of bias of the endpoints on symptomatology and health-related quality of life.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The dossier submitted by the pharmaceutical company underestimates the baseline incidence of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

In order to ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a basis in the resolution on the benefit assessment of daratumumab (resolution of 16 May 2024). A more valid estimate of the number of patients in the SHI target population is available here; this can be used despite continuing uncertainties.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of

product characteristics, SmPC) for Sarclisa (active ingredient: isatuximab) at the following publicly accessible link (last access: 24 June 2025):

https://www.ema.europa.eu/en/documents/product-information/sarclisa-epar-product-information_en.pdf

Treatment with isatuximab should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with multiple myeloma.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient identification card). The training material contains in particular information and warnings on how to manage the risk of isatuximab interfering with blood typing (indirect antihuman globulin test or indirect Coombs test). Isatuximab-induced interference with blood typing may persist for approximately 6 months after the last infusion of the medicinal product; therefore, healthcare professionals should advise patients to carry their patient identification card with them until 6 months after the end of treatment.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 July 2025).

The annual treatment costs shown refer to the first year of treatment.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The cost representation for isatuximab in combination with bortezomib, lenalidomide and dexamethasone is based on the treatment regimen used in the IMROZ study (EFC12522).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

Treatment period:

Adults with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Isatuximab in combination with bortezomib, lenalidomide and dexamethasone				
Isatuximab	42-day cycle: Cycle 1: Day 1, 8, 15, 22 and 29 Cycle 2 – 4: Day 1, 15 and 29 28-day cycle: From cycle 5 onwards Day 1 and 15	11.0	5 (cycle 1) 3 (cycle 2 – 4) 2 (from cycle 5)	28.0
Bortezomib	42-day cycle: Cycle 1 – 4 Day 1, 4, 8, 11, 22, 25, 29 and 32	4	8	32
Lenalidomide	42-day cycle: Cycle 1 – 4 Day 1 to 14 and Day 22 to 35 From cycle 5 onwards 28-day cycle Day 1 to 21	11.0	28 (cycle 1 – 4) 21 (from cycle 5)	259.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Dexamethasone PO / IV[2]	42-day cycle: Cycle 1 – 4 Day 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32 and 33 From cycle 5 onwards 28-day cycle Day 1, 8, 15 and 22	11.0	17 (cycle 1 – 4) 4 (from cycle 5)	96.0
Appropriate comparator therapy				
Daratumumab in combination with lenalidomide and dexamethasone				
Daratumumab	28-day cycle: Cycle 1 – 2: Day 1, 8, 15, 22 Cycle 3 – 6: Day 1 and 15 From cycle 7 onwards Day 1	13.0	4 (cycle 1 – 2) 2 (cycle 3 – 6) 1 (from cycle 7)	23.0
Lenalidomide	Day 1 - 21	13.0	21	273.0

[2] On the days of isatuximab administration, 20 mg of the dexamethasone dose is intravenously administered as premedication.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	28-day cycle			
Dexamethasone PO	Day 1, 8, 15, 22 28-day cycle	13.0	0 (cycle 1 – 2) 2 (cycle 3 – 6) 3 (from cycle 7)	29.0[3]
Daratumumab in combination with bortezomib, melphalan and prednisone				
Daratumumab	Cycle 1 6 x per 42-day cycle From cycle 2 onwards: 2 x per 42-day cycle	8.7	6 (cycle 1) 2 (from cycle 2)	21.4
Bortezomib	Cycle 1 8 x per 42-day cycle From cycle 2 onwards: 4 x per 42-day cycle	8.7	8 (cycle 1) 4 (from cycle 2)	38.8
Melphalan PO	Day 1 – 4 of the 42-day cycles	8.7	4	34.8
Prednisone PO	Day 2 – 4 of the 42-day cycles	8.7	3	26.1
Bortezomib in combination with melphalan and prednisone				

[3] On the days of daratumumab administration, 40 mg of the dexamethasone dose is used as premedication.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Bortezomib	Cycle 1 – 4 8 x per 42-day cycle From cycle 5 onwards: 4 x per 42-day cycle	8.7	8 (cycle 1 – 4) 4 (from cycle 5)	50.8
Melphalan	Day 1 – 4 of the 42-day cycles	8.7	4	34.8
Prednisone	Day 1 – 4 of the 42-day cycles	8.7	4	34.8
Bortezomib in combination with lenalidomide and dexamethasone				
Induction				
Bortezomib	On days 1, 4, 8 and 11 of a 21-day cycle	8	4	32
Lenalidomide	Day 1 – 14 of a 21-day cycle	8	14	112
Dexamethasone	On days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle	8	8	64
Follow-up treatment				
Lenalidomide	Day 1 – 21 of a 28-day cycle	7.0	21	147.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Dexamethasone	On days 1, 8, 15 and 22 of a 28-day cycle	7.0	4	28.0
Thalidomide in combination with melphalan and prednisone				
Thalidomide	Day 1 – 42 of a 42-day cycle	8.7	42	365.0
Melphalan	Day 1 – 4 of a 42-day cycle	8.7	4	34.8
Prednisone	Day 1 – 4 of a 42-day cycle	8.7	4	34.8
Bortezomib in combination with cyclophosphamide and dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Annex VI to Section K of the Pharmaceuticals Directive)				
Bortezomib	Day 1, 4, 8 and 11 of a 21-day cycle	17.4	4	69.6
Cyclophosphamide IV	Day 1 of a 21-day cycle	17.4	1	17.4
Dexamethasone PO	Day 1, 2, 4, 5, 8, 9, 11, 12 of a 21-day cycle	17.4	8	139.2

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body

weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916) [4].

As it is not always possible to achieve the exact calculated dose per day with the commercially available dosage strengths, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

Adults with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Isatuximab in combination with bortezomib, lenalidomide and dexamethasone[2]					
Isatuximab	10 mg/kg	777 mg	1 x 500 mg + 3 x 100 mg	28.0	28 x 500 mg + 84 x 100 mg
Bortezomib	1.3 mg/m²	2.5 mg	1 x 2.5 mg	32	32 x 2.5 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	259.0	259 x 25 mg
Dexamethasone PO	20 mg	20 mg	1 x 20 mg	68.0	68 x 20 mg
Dexamethasone IV	20 mg	20 mg	5 x 4 mg	28.0	140 x 4 mg
Appropriate comparator therapy					
Daratumumab in combination with lenalidomide and dexamethasone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	23	23 x 1,800 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273	273 x 25 mg

[4] Federal health reporting. Average body measurements of the population (2021, both sexes, 18 years and older), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Dexamethasone	40 mg	40 mg	40 mg	29	29 x 40 mg
Daratumumab in combination with bortezomib, melphalan and prednisone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	21.4	21.4 x 1,800 mg
Bortezomib	1.3 mg/m^2 = 2.5 mg	2.5 mg	1 x 2.5 mg	38.8	38.8 x 2.5 mg
Melphalan PO	9 mg/m^2 = 17.2 mg	17.2 mg	9 x 2 mg	34.8	313.2 x 2 mg
Prednisone PO	60 mg/m^2 = 114.6 mg	114.6 mg	2 x 50 mg + 1 x 10 mg + 1 x 5 mg	26.1	52.2 x 50 mg + 26.1 x 10 mg + 26.1 x 5 mg
Bortezomib in combination with melphalan and prednisone					
Bortezomib	1.3 mg/m^2 = 2.5 mg	2.5 mg	1 x 2.5 mg	50.8	50.8 x 2.5 mg
Melphalan	9 mg/m^2 = 17.2 mg	17.2 mg	9 x 2 mg	34.8	313.2 x 2 mg
Prednisone	60 mg/m^2 = 114.6 mg	114.6 mg	2 x 50 mg + 1 x 10 mg + 1 x 5 mg	34.8	69.6 x 50 mg + 34.8 x 10 mg + 34.8 x 5 mg
Bortezomib in combination with lenalidomide and dexamethasone					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Induction					
Bortezomib	1.3 mg/m^2 = 2.5 mg	2.5 mg	1 x 2.5 mg	32	32 x 2.5 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	112	112 x 25 mg
Dexamethasone PO	20 mg	20 mg	1 x 20 mg	64	64 x 20 mg
Follow-up treatment					
Lenalidomide	25 mg	25 mg	1 x 25 mg	147.0	147 x 25 mg
Dexamethasone PO	40 mg	40 mg	1 x 40 mg	28.0	28 x 40 mg
Thalidomide in combination with melphalan and prednisone					
Thalidomide	200 mg	200 mg	2 x 100 mg	365.0	730 x 100 mg
Melphalan	0.25 mg/kg = 19.4 mg	19.4 mg	10 x 2 mg	34.8	348 x 2 mg
Prednisone	2 mg/kg = 155.4 mg	155.4 mg	3 x 50 mg + 1 x 5 mg	34.8	104.4 x 50 mg + 34.8 x 5 mg
Bortezomib in combination with cyclophosphamide and dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Annex VI to Section K of the Pharmaceuticals Directive)					
Bortezomib	1.3 mg/m^2 = 2.5 mg	2.5 mg	1 x 2.5 mg	69.6	69.6 x 2.5 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Cyclophosphamide IV	900 mg/m² = 1,719 mg	1,719 mg	2 x 1,000 mg[5]	17.4	34.8 x 1,000 mg
Dexamethasone PO	40 mg	40 mg	1 x 40 mg	139.2	139.2 x 40 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Adults with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Isatuximab 500 mg	1 CIS	€ 1,621.58	€ 1.77	€ 89.32	€ 1,530.49
Isatuximab 100 mg	1 CIS	€ 333.96	€ 1.77	€ 17.86	€ 314.33
Lenalidomide 25 mg[7]	63 HC	€ 117.32	€ 1.77	€ 8.38	€ 107.17
Bortezomib 2.5 mg	1 PSI	€ 185.37	€ 1.77	€ 8.26	€ 175.34
Dexamethasone 20 mg[6]	50 TAB	€ 118.88	€ 1.77	€ 0.00	€ 117.11

[5] The administration form must be intravenous according to Annex VI of the Pharmaceuticals Directive.
[6] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Dexamethasone 4 mg[7]	10 SFI	€ 16.92	€ 1.77	€ 0.44	€ 14.71
Appropriate comparator therapy					
Bortezomib 2.5 mg	1 PSI	€ 185.37	€ 1.77	€ 8.26	€ 175.34
Cyclophosphamide 1,000 mg	6 PSI	€ 142.80	€ 1.77	€ 7.28	€ 133.75
Daratumumab 1,800 mg	1 SFI	€ 5,809.87	€ 1.77	€ 0.00	€ 5,808.10
Dexamethasone 40 mg[7]	50 TAB	€ 188.03	€ 1.77	€ 0.00	€ 186.26
Dexamethasone 20 mg[7]	50 TAB	€ 118.88	€ 1.77	€ 0.00	€ 117.11
Dexamethasone 20 mg[7]	20 TAB	€ 54.09	€ 1.77	€ 0.00	€ 52.32
Lenalidomide 25 mg[7]	63 HC	€ 117.32	€ 1.77	€ 8.38	€ 107.17
Melphalan 2 mg	50 FCT	€ 54.22	€ 1.77	€ 2.38	€ 50.07
Prednisone 50 mg[7]	50 TAB	€ 68.06	€ 1.77	€ 4.49	€ 61.80
Prednisone 10 mg[7]	100 TAB	€ 21.23	€ 1.77	€ 0.78	€ 18.68
Prednisone 5 mg[7]	100 TAB	€ 16.74	€ 1.77	€ 0.43	€ 14.54
Thalidomide 100 mg	30 CTA	€ 706.69	€ 1.77	€ 88.00	€ 616.92

Abbreviations: FCT = film-coated tablets; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PSI = powder for solution for injection; TAB = tablets; CTA = coated tablets

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Appropriate comparator therapy							
Daratumumab (in combination with lenalidomide and dexamethasone)							
Dexamethasone 40 mg, PO[7]	50 TAB x 40 mg	€ 188.03	€ 1.77	€ 0.00	€ 186.26	23	€ 85.68
Paracetamol 500 – 1,000 mg, PO[7,8]	20 TAB x 500 mg	€ 3.47	€ 0.17	€ 0.15	€ 3.15	23	€ 3.62
	10 TAB x 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01		€ 6.92
Dimetindene IV 1 mg/10 kg = 7.8 mg, IV	5 ILO x 4 mg	€ 26.24	€ 1.77	€ 6.92	€ 17.55	23	€ 161.46
Daratumumab (in combination with bortezomib, melphalan and prednisone)							
Dexamethasone 20 mg[7]	50 TAB x 20 mg	€ 118.88	€ 1.77	€ 0.00	€ 117.11	21.4	€ 50.12
Paracetamol 500 – 1,000 mg[7,8]	20 TAB (500 mg)	€ 3.47	€ 0.17	€ 0.15	€ 3.15	21.4	€ 3.37
	10 TAB (1,000 mg)	€ 3.32	€ 0.17	€ 0.14	€ 3.01		€ 6.44
Dimetindene IV 1 mg/10 kg = 7.8 mg, IV	5 ILO x 4 mg	€ 26.24	€ 1.77	€ 6.92	€ 17.55	21.4	€ 150.23

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Abbreviations: SFI = solution for injection; TAB = tablets							

Screening for hepatitis B virus (HBV)

Patients receiving therapy with daratumumab, thalidomide and lenalidomide should be tested for the presence of HBV infection before initiating the respective treatment.

Diagnostics to rule out chronic hepatitis B requires sensibly coordinated steps[7]. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. In certain case constellations, further steps may be necessary in accordance with current guideline recommendations.

In deviation from this, additional required SHI services are required for the diagnosis of suspected chronic hepatitis B, which usually differ between the medicinal product to be evaluated and the appropriate comparator therapy and are consequently considered as additionally required SHI services in the resolution.

Designation of the therapy	Designation of the service	Number	Unit cost	Costs/ patient/ year
Appropriate comparator therapy				
Daratumumab Lenalidomide Thalidomide	HBs antigen (GOP 32781)	1	€ 5.06	€ 5.06
	Anti-HBc antibody (GOP 32614)	1	€ 5.43	€ 5.43

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised

[7] S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011" https://register.awmf.org/assets/guidelines/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf

calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the

pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant

active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the

combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:

Product information for isatuximab (Sarclisa); SARCLISA 20 mg/ml concentrate for the preparation of an infusion solution; last revised: February 2025

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At their session on 28 November 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 5 February 2025 the pharmaceutical company submitted a dossier for the benefit assessment of isatuximab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 11 February 2025 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient isatuximab.

The dossier assessment by the IQWiG was submitted to the G-BA on 9 May 2025, and the written statement procedure was initiated with publication on the G-BA website on 15 May 2025. The deadline for submitting statements was 5 June 2025.

The oral hearing was held on 23 June 2025.

On 10 July 2025, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1 dated 10 July 2025 replaces version 1.0 of the dossier assessment dated 9 May 2025. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the Subcommittee on 29 July 2025, and the proposed draft resolution was approved.

At their session on 7 August 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	28 November 2023	Determination of the appropriate comparator therapy
Working group Section 35a	17 June 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	23 June 2025	Conduct of the oral hearing
Working group Section 35a	2 July 2025 16 July 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	29 July 2025	Concluding discussion of the draft resolution
Plenum	7 August 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 7 August 2025

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken